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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,778	ARACTINGI ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/20/06, 7/17/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 6/20/06 and 7/17/06 are acknowledged. Applicant's amendment filed 7/17/06 has been entered, and Applicant's amendment filed 6/20/06 has been entered in-part as it pertains to the portion that does not include the drawings.

2. Applicant is reminded of a election with traverse of Group I and species of HLA-G5 in Applicant's response filed 10/26/05. The Examiner had extended the search to include the species of soluble isoform comprising at least the α1 extracellular domain recited in now canceled claim 2.

Upon consideration of the prior art, the search has been extended to include the species recited in instant claims 13-16.

Claims 1, 3, 8 and 11-17 are currently being examined.

3. The disclosure is objected to because of the following informalities: The amendment filed 6/20/06 amends page 5 at line 37 to insert a Brief Description of the Drawings for Figures 1-5, however, there are 13 drawings. Appropriate correction is required.

The following are new grounds of rejection necessitated by Applicant's amendment filed 6/20/06.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 8 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the specification and claims as originally filed is as follows: "wherein the at least one soluble form of HLA-G is selected from the group consisting of the whole α1 extracellular domain of HLA-G".

Applicant points to support in originally filed claim 2; however, the originally filed disclosure is to "soluble isoforms of HLA-G comprising at least the α1 domain of HLA-G (page 6 at lines 31-35) and "comprising at least the α1 extracellular domain" (originally filed claim 2).

6. Claims 1, 3, 8 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a method for treating at least one inflammatory pathological skin condition, including psoriasis, in a subject comprising administering at least one soluble form of HLA-G, including those recited in the instant claims and at the recited concentrations, with at least one pharmaceutically acceptable vehicle. The specification has not enabled the breadth of the claimed invention because the claims encompass treating any inflammatory pathological skin condition, including psoriasis, with a soluble form of HLA-G. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the composition of the claimed method can be used to treat the said condition. The specification discloses no working examples with regards to the use of the instant invention for treatment of such a condition *in vivo*.

The specification discloses that psoriasis is a common chronic inflammatory pathology characterized by hyperproliferation of the keratinocytes of the epidermis (sentence spanning pages 4-5), that the dominant membrane-bound isoform HLA-G1 and the soluble isoform HLA-G5 are expressed only in inflammatory skin lesions [of psoriasis], whereas no HLA-G protein is detected in healthy skin (page 6 at lines 26-29), that macrophages in these lesions express HLA-G and infiltrating CD3+ T cells from these lesions express a receptor for inhibiting cytotoxic functions which is recognized by HLA-G, such as the ILT2 receptor (pages 6 at lines 18-24). The specification discloses that HLA-G isoforms comprising at least the α1 domain may inhibit the proliferative and cytotoxic functions of T lymphocytes (page 6 at lines 31-35). The specification further discloses that "soluble form of HLA-G" is intended to mean both the soluble HLA-Gs (not comprising a transmembrane domain) and the membrane-bound HLA-Gs which have been solubilized (page 7 at lines 29-34). The specification discloses that HLA-G can inhibit the activity of NK cells from peripheral blood or a CD8+ T cell line *in vitro* (Figures 4 and 5, brief description of the drawings).

Evidentiary reference Aractingi *et al* (The American J. of Pathology, July, 2001, Vol. 159, No. 1, pages 71-77, of record), said reference having a publication date after Applicant's effective filing date, teach that "Future analysis, such as functional studies in animal models, will be needed to ultimately assess the role of HLA-G in psoriasis" (last sentence of the article).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered, but are not persuasive.

The said arguments are of record in the amendment filed 6/20/06 on pages 6-7, briefly that: (1) the inventors have shown that HLA-G1 and HLA-G5 isoforms are expressed only in inflammatory lesions on macrophages located in the dermal papillae, whereas no HLA-G protein is detected in healthy skin, (2) infiltrating CD3+ T lymphocytes express a receptor, such as ILT2R, for inhibiting cytotoxic functions which is recognized by HLA-G, (3) an isoform of HLA-G comprising at least the α1 domain of HLA-G is capable of inhibiting the proliferative functions and the cytotoxic functions of T lymphocytes (figures 4 and 5), (4) taken together, the specification provides ample evidence of a nexus between HLA-G expression and inhibition of T lymphocytes, a common thread involved in various inflammatory skin conditions, psoriasis being only one example, (5) the evidentiary reference Aractingi *et al* does not provide any indication that HLA-G would not have the effect on inflammatory skin conditions, but rather that it will be necessary to dig deeper to understand the molecular basis for the mechanism of action.

It is the Examiner's position that: the demonstration of HLA-G protein in one type of inflammatory lesion, that of psoriasis patients, and of a receptor such as ILT2R on infiltrating CD3+ T lymphocytes that is recognized by HLA-G, and the demonstration that HLA-G can inhibit proliferative and cytotoxic functions of peripheral blood NK cells or a T cell line *in vitro* is not sufficient guidance for treating any inflammatory skin disorder, including psoriasis. It is the Examiner's further position that the evidentiary reference Aractingi *et al* teaches that "The soluble HLA-G molecule, that we identified in psoriasis, could therefore constitute at least one of the negative pathways that inhibit T-infiltrating cells." (last paragraph of article). Thus, the evidentiary reference teaches the possibility that soluble HLA-G could constitute at least one inhibitory pathway in psoriasis, out of others.

7. For the purpose of prior art rejections, the filing date of the instant claims 1, 3, 8 and 11-17 is deemed to be the filing date of the PCT/FR00/01670, *i.e.,* 6/16/00, because although a translation of the foreign priority document has now been supplied by Applicant, and the said document has support for a method for treating at last one inflammatory pathological skin condition, including psoriasis, in a subject comprising administering a composition comprising at least one soluble form of HLA-G, and at the concentration range recited in the instant claims, wherein the at least one soluble form of HLA-G is one that comprises at least the α1 domain, or that comprises one of HLA-G1, HLA-G2, HLA-G3, HLA-G5 or HLA-G5, the said document does not have support wherein the method uses a composition wherein the at least one soluble form of HLA-G *consists* of the whole α1 extracellular domain of HLA-G.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,753,625 (of record) as evidenced by admissions in the specification at the paragraph spanning pages 4 and 5.

U.S. Patent No. 5,753,625 discloses administering a pharmaceutical composition comprising a peptide having the sequence of MHC class I antigen α1 domain such as that of HLA-G to treat autoimmune diseases such as psoriasis (especially abstract, column 1 at the second full paragraph, column 2 at lines 40-46 and lines 57-67, column 3 at lines 1-3, column 4 at lines 22-24, column 5 at lines 50-63).

The admissions in the specification at the paragraph spanning pages 4 and 5 are that psoriasis is a chronic inflammatory pathology that is characterized by hyperproliferation of the keratinocytes of the epidermis or skin.

Applicant's arguments have been fully considered, but are not persuasive.

The said arguments are of record in the amendment filed 6/20/06 on pages 7-8, briefly, that '625 does not describe the treatment of inflammatory conditions, including psoriasis, with the whole α1 domain of soluble HLA-G, (2) that '625 discloses using the specific fragment aa 70-91 of class I, '625 describes specific peptides of this type, and they must always have a valine at position 76, whereas the methionine is present at this position in HLA-G, IDDM is the only disease exemplified in the examples, and acknowledging psoriasis is an inflammatory pathology does not provide the disclosure to devise and select the treatment.

It is the Examiners position that: '625 does teach the treatment of psoriasis using at least part, but also including the entire α1 domain of class I molecules, including of HLA-G, and discloses that the α1 domain includes the amino acid residues between positions 70 and 91 of MHC class I. It is the Examiner's further position that '625 discloses that one group of therapeutic compositions comprise a peptide from HLA-B class I molecules' α1 domain and that is the peptide that Applicant is arguing has a valine at position 76; however, '625 discloses that for a given locus, the amino acid sequence of this region has several invariant residues, and is otherwise generally conserved among different alleles. '625 discloses that HLA-A, -B, -C, -E and –G as well as murine H-2K and H-2D are antigens of interest. It is the Examiner's position that although the treatment of psoriasis using the α1 domain of HLA-G is not exemplified, '625 discloses using the α1 domain of HLA-G for treatment of psoriasis, and teaches that psoriasis is a disease of interest to be treated with the peptides of the invention. It is the Examiner's position that the admissions in the specification that psoriasis is a chronic inflammatory pathology characterized by hyperproliferation of keratinocytes in the epidermis or skin is not relied upon for devising and selecting treatment, but rather is an admission that psoriasis is an inflammatory pathological skin condition such as recited in the instant claims, the disclosure of '625 to the treatment of psoriasis using the α1 domain of HLA-G.

10. Claims 1, 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,753,625 (of record) as evidenced by admissions in the specification at the paragraph spanning pages 4 and 5.

U.S. Patent No. 5,753,625 discloses administering a pharmaceutical composition comprising a peptide having the sequence of MHC class I antigen α1 domain such as that of HLA-G to treat autoimmune diseases such as psoriasis (especially abstract, column 1 at the second full paragraph, column 2 at lines 40-46 and lines 57-67, column 3 at lines 1-3, column 4 at lines 22-24, column 5 at lines 50-63).

The admissions in the specification at the paragraph spanning pages 4 and 5 are that psoriasis is a chronic inflammatory pathology that is characterized by hyperproliferation of the keratinocytes of the epidermis or skin.

Applicant's arguments have been fully considered, but are not persuasive.

The said arguments are of record in the amendment filed 6/20/06 on pages 7-8, briefly, that '625 does not describe the treatment of inflammatory conditions, including psoriasis, with the whole α1 domain of soluble HLA-G, (2) that '625 discloses using the specific fragment aa 70-91 of class I, '625 describes specific peptides of this type, and they must always have a valine at position 76, whereas the methionine is present at this position in HLA-G, IDDM is the only disease exemplified in the examples, and acknowledging psoriasis is an inflammatory pathology does not provide the disclosure to devise and select the treatment.

It is the Examiners position that: '625 does teach the treatment of psoriasis using at least part, but also including the entire α1 domain of class I molecules, including of HLA-G, and discloses that the α1 domain included the amino acid residues between positions 70 and 91 of MHC class I. It is the Examiner's further position that '625 discloses that one group of therapeutic compositions comprise a peptide from HLA-B class I molecules' α1 domain and that is the peptide that Applicant is arguing has a valine at position 76; however, '625 discloses that for a given locus, the amino acid sequence of this region has several invariant residues, and is otherwise generally conserved among different alleles. '625 discloses that HLA-A, -B, -C, -E and –G as well as murine H-2K and H-2D are antigens of interest. It is the Examiner's position that although the treatment of psoriasis using the α1 domain of HLA-G is not exemplified, '625 discloses using the α1 domain of HLA-G for treatment of psoriasis, and teaches that psoriasis is a disease of interest to be treated with the peptides of the invention. It is the Examiner's position that the admissions in the specification that psoriasis is a chronic inflammatory pathology characterized by hyperproliferation of keratinocytes in the epidermis or skin is not relied upon for devising and selecting treatment, but rather is an admission that psoriasis is an inflammatory pathological skin condition such as recited in the instant claims, the disclosure of '625 to the treatment of psoriasis using the α1 domain of HLA-G.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 3, 8, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,753,625 (of record) in view of U.S. Patent No. 5,417,986 (of record) and admissions in the specification at the paragraph spanning pages 4 and 5.

U.S. Patent No. 5,753,625 discloses administering a pharmaceutical composition comprising a peptide having the sequence of MHC class I antigen α1 do main such as that of HLA-G to treat autoimmune diseases such as psoriasis. U.S. Patent No. 5,753,625 discloses that the dosage of the therapeutic formulation will vary widely depending upon the nature of the disease, the frequency of administration, the manner of administration, the clearance of the agent from the host, and that the initial dose may be larger followed by smaller maintenance doses, for example, using from 1 to 100 mg/kg body weight to treat an autoimmune disease (especially abstract, column 1 at the second full paragraph, column 2 at lines 40-46 and lines 57-67, column 3 at lines 1-3, column 4 at lines 22-24, column 5 at lines 50-63, column 7 at lines 17-36).

U.S. Patent No. 5,753,625 does not disclose that the concentration of the at least one soluble form of HLA-G is between 0.1 and 5 ug/ml (recited in instant claim 3), nor between 0.5 and 2.5 ug/ml (recited in instant claim 8).

U.S. Patent No. 5,417,986 discloses IV injection of peptides into primates at a concentration of 0.6 ug/ml, or s.c. injection of polypeptide into mice at 5 ug/ml (especially column 15 at lines 54-56 and column 40 at lines 34-40, respectively).

The admissions in the specification at the paragraph spanning pages 4 and 5 are that psoriasis is a chronic inflammatory pathology that is characterized by hyperproliferation of the keratinocytes of the epidermis or skin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have treated psoriasis, disclosed to be a chronic inflammatory skin condition by admissions in the specification, with a pharmaceutical composition comprising the α1 domain of HLA-G as disclosed by U.S. Patent No. 5,753,625 using the concentrations disclosed by U.S. Patent No. 5,417,986.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because U.S. Patent No. 5,753,625 does not disclose that the concentration of the HLA-G α1 domain polypeptide and U.S. Patent No. 5,417,986 discloses concentrations of polypeptides suitable for *in vivo* administration for treating primates, *i.e.,* including humans, or mice.

Applicant's arguments have been fully considered, but are not persuasive.

The said arguments are of record in the amendment filed 6/20/06 on pages 8-9, briefly that '986 does not compensate for the deficiencies of '625, the combination does not describe or suggest all of the claim limitations, and '986 relates to vaccines and is not generally applicable to the treatment of autoimmune conditions disclose in '625.

It is the Examiner's position that: the Examiner's position with regard to the disclosure of '625 and Applicant's arguments thereto enunciated supra apply herein, '986 teaches *concentration*, not dosage amount, and as such is being relied upon for that disclosure of concentration suitable for administration to primates or mice, and '625 discloses that the dosage amount of the therapeutic formulation will vary widely depending upon the nature of the disease, the frequency of administration, the manner of administration, and the clearance of the agent from the host. It is the Examiner's further position that the instant claims do not recite a dosage amount, but rather recite a concentration.

13. Claims 1 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,753,625 (of record) in view of WO 98/37098 A1 (Applicant's IDS reference) and admissions in the specification at the paragraph spanning pages 4 and 5.

U.S. Patent No. 5,753,625 discloses administering a pharmaceutical composition comprising a peptide having the sequence of MHC class I antigen α1 do main such as that of HLA-G to treat autoimmune diseases such as psoriasis. U.S. Patent No. 5,753,625 discloses that the dosage of the therapeutic formulation will vary widely depending upon the nature of the disease, the frequency of administration, the manner of administration, the clearance of the agent from the host, and that the initial dose may be larger followed by smaller maintenance doses, for example, using from 1 to 100 mg/kg body weight to treat an autoimmune disease (especially abstract, column 1 at the second full paragraph, column 2 at lines 40-46 and lines 57-67, column 3 at lines 1-3, column 4 at lines 22-24, column 5 at lines 50-63, column 7 at lines 17-36).

U.S. Patent No. 5,753,625 does not disclose administering a solubilized form of HLA-G1, HLA-G2, HLA-G3, HLA-G3, HLA-G4, nor HLA-G5 for treating an inflammatory pathological skin condition.

WO 98/37098 A1 teaches isoforms of HLA-G that include the α1 domain are HLA-G1, HLA-G2, HLA-G3, HLA-G4 and HLA-G5. WO 98/37098 A1 further teaches soluble isoforms of HLA-G5 and incubating NK cells or ligands with HLA-G, or making a immunomodulating composition comprising an isoform of HLA-G for inhibiting the activity of NK cells to treat autoimmune diseases (especially abstract, pages 1-7).

The admissions in the specification at the paragraph spanning pages 4 and 5 are that psoriasis is a chronic inflammatory pathology that is characterized by hyperproliferation of the keratinocytes of the epidermis or skin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered any solublilized form of HLA-G comprising the α1 domain such as HLA-G1, HLA-G2, HLA-G3, HLA-G4 and HLA-G5 taught by WO 98/37098 A1 in a pharmaceutical composition such as that disclosed by U.S. Patent No. 5,753,625 to treat psoriasis, disclosed to be a chronic inflammatory skin condition by admissions in the specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat psoriasis because U.S. Patent No. 5,753,625 discloses administering a pharmaceutical composition comprising a peptide having the sequence of MHC class I antigen α1 domain such as that of HLA-G to treat autoimmune diseases such as psoriasis, and WO 98/37098 A1 teaches isoforms of HLA-G that include the α1 domain, including the soluble isoform of HLA-G5, and teaches administering them to treat autoimmune diseases.

Applicant's arguments have been fully considered, but are not persuasive.

The said arguments are of record in the amendment filed 6/20/06 on pages 9-10, briefly, that the disclosure of the WO document relates to the expression of HLA-G genes on the cell surface and use for inhibiting the activity of NK cells, that the '625 patent does not teach using the whole α1 domain or the whole soluble HLA-G for treatment of inflammatory skin conditions such as psoriasis, and that using the whole soluble isoform would go directly against the teachings of '625.

It is the Examiner's position that the (translation of the) WO document (provided by Applicant on 6/20/06) discloses secreted HLA-G isoforms comprising at least the α1 domain (page 5, last para., page 6 first para), the production of soluble HLA-G isoforms by isolating them from the cell surface or by cloning them (lines 22-35 on page 8), the importance of the α1 domain plays in protection against NK cells and that the KIR receptor on NK cells binds to the α1 domain of MHC class I (page 25, last para), and that soluble HLA-G5, like other isoforms, inhibits cytolytic activity of NK cells (page 27 at lines 5-8). It is the Examiner's further position that the Examiner's reply to Applicant's arguments to the disclosure of '625 supra apply herein, that '625 does not disclose that the entire soluble HLA-G isoform should not be administered, nor that it would not produce the desired activity, and the WO document teaches that soluble isoforms that comprise the α1 domain important for reactivity with NK cell receptors can produce the desired activity of inhibiting NK cell cytolytic activity.

14. Claims 3 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,753,625 (of record) in view of WO 98/37098 A1 (Applicant's IDS reference) and admissions in the specification at the paragraph spanning pages 4 and 5 as applied to claims 1 and 11-17 above, and further in view of U.S. Patent No. 5,417,986 (of record).

The combination of U.S. Patent No. 5,753,625, WO 98/37098 A1 (Applicant's IDS reference) and admissions in the specification at the paragraph spanning pages 4 and 5 have been discussed supra, hereafter referred to as "the combined references."

The combined references do not disclose that the concentration of the at least one soluble form of HLA-G is between 0.1 and 5 ug/ml (recited in instant claim 3), nor between 0.5 and 2.5 ug/ml (recited in instant claim 8).

U.S. Patent No. 5,417,986 discloses IV injection of peptides into primates at a concentration of 0.6 ug/ml, or s.c. injection of polypeptide into mice at 5 ug/ml (especially column 15 at lines 54-56 and column 40 at lines 34-40, respectively).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have treated psoriasis, disclosed to be a chronic inflammatory skin condition by admissions in the specification, with a pharmaceutical composition comprising a soluble isoform of HLA-G consisting of or comprising the α1 domain of HLA-G as disclosed by the combined references using the concentrations disclosed by U.S. Patent No. 5,417,986.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because the combined references do not disclose that the concentration of the HLA-G α1 domain polypeptide and U.S. Patent No. 5,417,986 discloses concentrations of polypeptides suitable for *in vivo* administration for treating primates or mice.

Applicant's does not address this rejection in the amendment filed 6/20/06.

However, it is the Examiner's position that: the Examiner's position with regard to the disclosure of '625 and Applicant's arguments thereto enunciated supra apply herein, '986 teaches *concentration*, not dosage amount, and as such is being relied upon for that teaching of concentration suitable for administration to primates or mice, and '625 discloses that the dosage amount of the therapeutic formulation will vary widely depending upon the nature of the disease, the frequency of administration, the manner of administration, and the clearance of the agent from the host. It is the Examiner's further position that the instant claims do not recite a dosage amount, but rather recite a concentration.

15. Claim 1 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,753,625(of record) in view of WO 98/37098 A1 (Applicant's IDS reference), US 2003/0162175 A1 (of record) and admissions in the specification at the paragraph spanning pages 4 and 5.

U.S. Patent No. 5,753,625 discloses administering a pharmaceutical composition comprising a peptide having the sequence of MHC class I antigen α1 do main such as that of HLA-G to treat autoimmune diseases such as psoriasis. U.S. Patent No. 5,753,625 discloses that the dosage of the therapeutic formulation will vary widely depending upon the nature of the disease, the frequency of administration, the manner of administration, the clearance of the agent from the host, and that the initial dose may be larger followed by smaller maintenance doses, for example, using from 1 to 100 mg/kg body weight to treat an autoimmune disease (especially abstract, column 1 at the second full paragraph, column 2 at lines 40-46 and lines 57-67, column 3 at lines 1-3, column 4 at lines 22-24, column 5 at lines 50-63, column 7 at lines 17-36).

U.S. Patent No. 5,753,625 does not disclose administering a solubilized form of HLA-G1, HLA-G2, HLA-G3, HLA-G3, HLA-G4, nor HLA-G5 for treating an inflammatory pathological skin condition.

WO 98/37098 A1 teaches isoforms of HLA-G that include the α1 domain are HLA-G1, HLA-G2, HLA-G3, HLA-G4 and HLA-G5. WO 98/37098 A1 further teaches soluble isoforms of HLA-G5 and incubating NK cells or ligands with HLA-G, or making a immunomodulating composition comprising an isoform of HLA-G for inhibiting the activity of NK cells to treat autoimmune diseases (especially abstract, pages 1-7).

US 2003/0162175 A1 discloses that NK cell have two functional types of MHC class I specific receptors, activation receptors and inhibitory receptors, the latter KIR include ILT1, -2, -3, -4 and –5. US 2003/0162175 A1 further discloses that NK cells are inhibited by HLA-G, and that NK cells appear to regulate autoimmunity. US 2003/0162175 A1 discloses using pharmaceutical compositions comprising NKCR (NK Cell Receptor) polypeptides to ameliorate autoimmunity or inflammation. US 2003/0162175 A1 discloses that psoriasis is a disorder that may be treated with the polypeptides (especially [0003], [0004], [0013], [0017], [0019], [0620] and [0642]).

The admissions in the specification at the paragraph spanning pages 4 and 5 are that psoriasis is a chronic inflammatory pathology that is characterized by hyperproliferation of the keratinocytes of the epidermis or skin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered any solublilized form of HLA-G comprising the α1 domain such as HLA-G1, HLA-G2, HLA-G3, HLA-G4 and HLA-G5 taught by WO 98/37098 A1 in a pharmaceutical composition such as that disclosed by U.S. Patent No. 5,753,625 to treat psoriasis, particularly in light of the disclosure of US 2003/0162175 A1 that NK cells are inhibited by HLA-G and psoriasis is a disease to be treated with NKCR inhibitory polypeptides, and the admissions in the specification are that psoriasis is an inflammatory pathological condition of the skin.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat psoriasis because U.S. Patent No. 5,753,625 discloses administering a pharmaceutical composition comprising a peptide having the sequence of MHC class I antigen α1 domain such as that of HLA-G to treat autoimmune diseases such as psoriasis, WO 98/37098 A1 teaches isoforms of HLA-G that include the α1 domain, including the soluble isoform of HLA-G5, and teaches administering them to treat autoimmune diseases, and US 2003/0162175 A1 discloses that psoriasis is a disease to be treated with NKCR inhibitory polypeptides and that HLA-G inhibits NK cells.

Applicant's arguments have been fully considered, but are not persuasive.

The said arguments are of record in the amendment filed 6/20/06 on page 10, briefly, that '175 has priority to 12/22/99, whereas the instant claims have priority to the filing date of the foreign priority document, *i.e.,* 6/18/99.

The Examiner's position is that the instant claims have a priority date of 6/16/00 as enunciated supra.

16. Claims 3 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,753,625 (of record) in view of WO 98/37098 A1 (Applicant's IDS reference), US 2003/0162175 A1 (of record) and admissions in the specification at the paragraph spanning pages 4 and 5 as applied to claims 1 and 11-17 above, and further in view of U.S. Patent No. 5,417,986 (of record) .

The combination of U.S. Patent No. 5,753,625, WO 98/37098 A1 (Applicant's IDS reference), US 2003/0162175 A1 and admissions in the specification at the paragraph spanning pages 4 and 5 have been discussed supra, hereafter referred to as "the combined references."

The combined references do not disclose that the concentration of the at least one soluble form of HLA-G is between 0.1 and 5 ug/ml (recited in instant claim 3), nor between 0.5 and 2.5 ug/ml (recited in instant claim 8).

U.S. Patent No. 5,417,986 discloses IV injection of peptides into primates at a concentration of 0.6 ug/ml, or s.c. injection of polypeptide into mice at 5 ug/ml (especially column 15 at lines 54-56 and column 40 at lines 34-40, respectively).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have treated psoriasis, disclosed to be a chronic inflammatory skin condition by admissions in the specification, with a pharmaceutical composition comprising a soluble isoform of HLA-G consisting of or comprising the α1 domain of HLA-G as disclosed by the combined references using the concentrations disclosed by U.S. Patent No. 5,417,986.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because the combined references do not disclose that the concentration of the HLA-G α1 domain polypeptide and U.S. Patent No. 5,417,986 discloses concentrations of polypeptides suitable for *in vivo* administration for treating primates or mice.

Applicant does not traverse this rejection in the amendment filed 6/20/06.

However, it is the Examiner's position that that the instant claims have a priority date of 6/16/00 as enunciated supra.

17. No claim is allowed.

18. Claim 3 is objected to because of the following informality: There is a spelling error at line 2, *i.e.,* 5 ug/m should be 5 ug/ml. Appropriate correction is required.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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